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REPLY UNDER 37 CFR § 1.116
EXPEDITED PROCEDURE

PATENT
Docket No.: R1390-00003
[Former Docket No.: 8223.002.CPUS02]
Client Ref.: Archimedes, Inc.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Leonard SCHLESSINGER, et al.	Confirmation No.: 8542
Serial No.: 10/763,653	Group Art Unit: 1631
Filing Date: January 12,2004	Examiner: Jason M. Sims
Title: GENERATING A MATHEMATICAL MODEL FOR DIABETES	

REPLY TO FINAL OFFICE ACTION UNDER 37 CFR § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This is in reply to the Office Action dated September 11, 2008, Paper No. 20080903, for which a reply is due on December 11, 2008. This reply is filed within two months of the issuance of the final Office Action and therefore qualifies for expedited review. Accordingly, this reply is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested. Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

The **Remarks** begin on page 11 of this paper.

The **Conclusion** begins on page 18 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Claim 1 (previously presented): A method for estimating a virtual patient's fasting plasma glucose (FPG) level, comprising:

determining the virtual patient's basal hepatic production (FPG_0);

determining the virtual patient's insulin level (I);

calculating the virtual patient's FPG at time t by solving an equation

$FPG(t) = FPG_0 / (I * E)$, wherein E is a value representing efficiency of insulin use; and

outputting at least one value for the virtual patient's FPG at time t to a user.

Claim 2 (previously presented): The method of claim 1, wherein E is scaled such that $E = 1$ in the absence of diabetes and $0 \leq E < 1$ in the presence of diabetes.

Claim 3 (currently amended): The method of claim 1, wherein for type 2 diabetes, an equation representing E is:

$E(DF_2) = \left(a + b / \left(1 + (DF_2 / c)^d\right)\right)^{\frac{1}{2}}$, wherein the parameters a, b, c, and d are set to fit data <u>for E and DF_2</u> for a population that is represented by the virtual patient, and DF_2 ~~is a type 2 diabetes feature that~~ represents an incidence of type 2 diabetes for the virtual patient<u>, so that values of DF_2 above a threshold value correspond to an occurrence of type 2 diabetes in the virtual patient</u>.

Claim 4 (currently amended): The method of claim 3, wherein

$$DF_2(t) = \left(1 - \exp\left(-a_1 * IGT(\xi_3) / \left(1 + \exp\left(-\frac{(t - b_1)}{c_1}\right)\right)\right)\right) * RBMI(BMI) / \xi_2$$, wherein ξ_2 and ξ_3 are random values selected from distributions for randomizing the virtual patient within the population, IGT is an impaired glucose tolerance value indexed by the random value ξ_3, RBMI is a relative risk associated with the virtual patient's body mass index (BMI), and the parameters a_1,

b_1, and c_1, are set to fit data for DF_2 and t for the population that is represented by the virtual patient.

Claim 5 (currently amended): The method of claim 4, wherein the *RBMI* is represented by:

$RBMI(BMI) = a_2 + b_2 / \left(1 + e^{-(BMI - c_2)/d_2}\right)$, and the parameters a_2, b_2, c_2, and d_2, are set to fit data for RBMI and BMI for the population that is represented by the virtual patient.

Claim 6 (previously presented): The method of claim 4, wherein *IGT* is represented by:

$IGT(\xi_3) = 2(1 - \xi_3)$

wherein the random value ξ_3 is designed so that the occurrence of diabetes corresponds to variations that occur in the population that is represented by the virtual patient.

Claim 7 (currently amended): The method of claim 1, wherein said determining said virtual patient's basal hepatic production in type 2 diabetes includes solving an equation $FPG_0(t) = G(t) * H(DF_2(t))$, wherein $G(t)$ represent a basal production in people who do not have diabetes, H represents a degree of insulin resistance in a person with diabetes, and DF_2 ~~is a type 2 diabetes feature that~~ represents an incidence of type 2 diabetes for the virtual patient, so that values of DF_2 above a threshold value correspond to an occurrence of type 2 diabetes in the virtual patient.

Claim 8 (currently amended): The method of claim 7, wherein $H(DF_2(t)) = 1/\left(MAX\left[E^2(DF_2(t+a)), b\right]\right)$, and the parameters a and b are set to fit data for H and DF_2 for a population that is represented by the virtual patient.

Claim 9 (currently amended): The method of claim 7, wherein $G(t) = \left(a + bt^{1.5} - c * t^3 + \Delta_g\right) / \left(d - e \exp\left(-DF_2(t)\xi_2\right)\right)$, wherein Δ_g represents a variance of basal hepatic production across individuals, the parameters a, b, c, d, and e are set to fit data for G and t for a population that is represented by the virtual patient, and ξ_2 is a random value selected from a distribution for randomizing the virtual patient within the population.

Claim 10 (currently amended): The method of claim l, wherein $I(DF_1, DF_2) = H(DF_2) * E(DF_2) / \left(1 + \exp\left((DF_1 - a)/b\right)\right)$, and wherein DF_1 ~~is a type 1 diabetes feature that~~ represents an incidence of type 1 diabetes for the virtual patient so that values of DF_1 above a first threshold value correspond to an occurrence of type 1 diabetes in the virtual patient, DF_2 ~~is a type 2 diabetes feature that~~ represents an incidence of type 2 diabetes for the virtual patient so that values of DF_2 above a second threshold value correspond to an occurrence of type 2 diabetes in the virtual patient, H represents a degree of insulin resistance in a person with diabetes, and the parameters a and b are set to fit data for I, DF_1 and DF_2 for a population that is represented by the virtual patient.

Claims 11-30 (canceled).

Claim 31 (previously presented): An apparatus for estimating a virtual patient's fasting plasma glucose (FPG) level, the apparatus comprising:

means for determining the virtual patient's basal hepatic production (FPG_0);

means for determining the virtual patient's insulin level (I);

means for calculating the virtual patient's FPG at time t by solving an equation $FPG(t) = FPG_0 / (I * E)$, wherein E is a value representing efficiency of insulin use; and

means for outputting at least one value for the virtual patient's FPG at time t to a user.

Claim 32 (previously presented): The apparatus of claim 31, wherein E is scaled such that $E = 1$ in the absence of diabetes and $0 \leq E < 1$ in the presence of diabetes.

Claim 33 (currently amended): The apparatus of claim 31, wherein for type 2 diabetes, an equation representing E is:

$E(DF_2) = \left(a + b / \left(1 + (DF_2 / c)^d\right)\right)^{\frac{1}{2}}$, wherein the parameters a, b, c, and d are set to fit data for E and DF_2 for a population that is represented by the virtual patient, and DF_2 ~~is a type 2 diabetes feature that~~ represents an incidence of type 2 diabetes for the virtual patient, so that values of DF_2 above a threshold value correspond to an occurrence of type 2 diabetes in the virtual patient.

Claim 34 (currently amended): The apparatus of claim 33, wherein

$DF_2(t) = \left(1 - \exp\left(-a_1 * IGT(\xi_3) / \left(1 + \exp\left(-\frac{(t - b_1)}{c_1}\right)\right)\right)\right) * RBMI(BMI) / \xi_2$, wherein ξ_2 and ξ_3 are random values selected from distributions for randomizing the virtual patient within the population, *IGT* is an impaired glucose tolerance value indexed by the random value ξ_3, RBMI is a relative risk associated with the virtual patient's body mass index (BMI), and the parameters a_1, b_1, and c_1, are set to fit data for DF_2 and t for the population that is represented by the virtual patient.

Claim 35 (currently amended): The apparatus of claim 33, wherein the *RBMI* is represented by:

$RBMI(BMI) = a_2 + b_2 / \left(1 + e^{-(BMI - c_2)/d_2}\right)$, and the parameters a_2, b_2, c_2, and d_2, are set to fit data for RBMI and BMI for the population that is represented by the virtual patient.

Claim 36 (previously presented): The apparatus of claim 34, wherein *IGT* is represented by: $IGT(\xi_3) = 2(1 - \xi_3)$,

wherein the random value ξ_3 is designed so that the occurrence of diabetes corresponds to variations that occur in the population that is represented by the virtual patient.

Claim 37 (currently amended): The apparatus of claim 31, wherein said means for determining said virtual patient's basal hepatic production in type 2 diabetes includes means for solving an equation $FPG_0(t) = G(t) * H(DF_2(t))$, wherein $G(t)$ represent a basal production in people who do not have diabetes, H represents a degree of insulin resistance in a person with diabetes, and DF_2 ~~is a type 2 diabetes feature that~~ represents an incidence of type 2 diabetes for the virtual patient, so that values of DF_2 above a threshold value correspond to an occurrence of type 2 diabetes in the virtual patient.

Claim 38 (currently amended): The apparatus of claim 37,wherein $H(DF_2(t)) = 1 / \left(MAX\left[E^2(DF_2(t + a)), b\right]\right)$, and the parameters a and b are set to fit data for H and DF_2 for a population that is represented by the virtual patient.

Claim 39 (currently amended): The apparatus of claim 37, wherein

$G(t) = \left(a + bt^{1.5} - c*t^3 + \Delta_g\right) / \left(d - e\exp\left(-DF_2(t)\xi_2\right)\right)$, wherein Δ_g represents a variance of basal hepatic production across individuals, the parameters a, b, c, d, and e are set to fit data for G and t for a population that is represented by the virtual patient, and ξ_2 is a random value selected from a distribution for randomizing the virtual patient within the population.

Claim 40 (currently amended): The apparatus of claim 31, wherein

$I(DF_1, DF_2) = H(DF_2) * E(DF_2) / \left(1 + \exp\left((DF_1 - a)/b\right)\right)$, and wherein DF_1 ~~is a type 1 diabetes feature that~~ represents an incidence of type 1 diabetes for the virtual patient so that values of DF_1 above a first threshold value correspond to an occurrence of type 1 diabetes in the virtual patient, DF_2 ~~is a type 2 diabetes feature that~~ represents an incidence of type 2 diabetes for the virtual patient so that values of DF_2 above a second threshold value correspond to an occurrence of type 2 diabetes in the virtual patient, H represents a degree of insulin resistance in a person with diabetes, and the parameters a and b are set to fit data for I, DF_1 and DF_2 for a population that is represented by the virtual patient.

Claims 41-51 (canceled).

Claim 52 (previously presented): A program storage device readable by a machine, tangibly embodying a program of instructions executable by the machine to perform a method for estimating a virtual patient's fasting plasma glucose (FPG) level, the method comprising:

determining the virtual patient's basal hepatic production (FPG_0);

determining the virtual patient's insulin level (I);

calculating the virtual patient's FPG at time t by solving an equation

$FPG(t) = FPG_0 / (I * E)$, wherein E is a value representing efficiency of insulin use; and

outputting at least one value for the virtual patient's FPG at time t to a user.

Claims 53-60 (canceled).

Claim 61 (previously presented): The method of claim 1, wherein the at least one value based on the virtual patient's FPG at time t is saved in at least one file in a computer storage device.

Claim 62 (previously presented): The method of claim 3, further comprising:

setting values for the parameters a, b, c, and d by fitting the equation representing E to data for the population according to a least-squares criterion.

Claim 63 (previously presented): The apparatus of claim 31, wherein the at least one value based on the virtual patient's FPG at time t is saved to a computer-readable medium.

Claim 64 (previously presented): The apparatus of claim 33, further comprising:

means for setting values for the parameters a, b, c, and d by fitting the equation representing E to data for the population according to a least-squares criterion.

Claim 65 (previously presented): The program storage device of claim 52, wherein E is scaled such that $E = 1$ in the absence of diabetes and $0 \leq E < 1$ in the presence of diabetes.

Claim 66 (currently amended): The program storage device of claim 52, wherein for type 2 diabetes, an equation representing E is:

$E(DF_2) = \left(a + b/\left(1 + (DF_2/c)^d\right)\right)^{\frac{1}{2}}$, wherein the parameters a, b, c, and d are set to fit data for E and DF_2 for a population that is represented by the virtual patient, and DF_2 ~~is a type 2 diabetes feature that~~ represents an incidence of type 2 diabetes for the virtual patient, so that values of DF_2 above a threshold value correspond to an occurrence of type 2 diabetes in the virtual patient.

Claim 67 (currently amended): The program storage device of claim 66, wherein

$DF_2(t) = \left(1 - \exp\left(-a_1 * IGT(\xi_3) / \left(1 + \exp\left(-\frac{(t - b_1)}{c_1}\right)\right)\right)\right) * RBMI(BMI)/\xi_2$, wherein ξ_2 and ξ_3 are random values selected from distributions for randomizing the virtual patient within the population, *IGT* is an impaired glucose tolerance value indexed by the random value ξ_3, RBMI is a relative risk associated with the virtual patient's body mass index (BMI), and the parameters a_1, b_1, and c_1, are set to fit data for DF_2 and t for the population that is represented by the virtual patient.

Claim 68 (currently amended): The program storage device of claim 67, wherein the *RBMI* is represented by:

$RBMI(BMI) = a_2 + b_2 / \left(1 + e^{-(BMI - c_2)/d_2}\right)$, and the parameters a_2, b_2, c_2, and d_2, are set to fit data for RBMI and BMI for the population that is represented by the virtual patient.

Claim 69 (previously presented): The program storage device of claim 67, wherein *IGT* is represented by:

$IGT(\xi_3) = 2(1 - \xi_3)$

wherein the random value ξ_3 is designed so that the occurrence of diabetes corresponds to variations that occur in the population that is represented by the virtual patient.

Claim 70 (currently amended): The program storage device of claim 52, wherein said determining said virtual patient's basal hepatic production in type 2 diabetes includes solving an equation $FPG_0(t) = G(t) * H(DF_2(t))$, wherein *G*(t) represent a basal production in people who do not have diabetes, H represents a degree of insulin resistance in a person with diabetes, and DF_2 ~~is a type 2 diabetes feature that~~ represents an incidence of type 2 diabetes for the virtual patient, so that values of DF_2 above a threshold value correspond to an occurrence of type 2 diabetes in the virtual patient.

Claim 71 (currently amended): The program storage device of claim 70, wherein $H(DF_2(t)) = 1/\left(MAX\left[E^2(DF_2(t+a)), b\right]\right)$, and the parameters a and b are set to fit data for H and DF_2 for a population that is represented by the virtual patient.

Claim 72 (currently amended): The program storage device of claim 70, wherein $G(t) = \left(a + bt^{1.5} - c * t^3 + \Delta_g\right) / \left(d - e \exp\left(-DF_2(t)\xi_2\right)\right)$, wherein Δ_g represents a variance of basal hepatic production across individuals, the parameters a, b, c, d, and e are set to fit data for G and t for a population that is represented by the virtual patient, and ξ_2 is a random value selected from a distribution for randomizing the virtual patient within the population.

Claim 73 (currently amended): The program storage device of claim 52, wherein $I(DF_1, DF_2) = H(DF_2) * E(DF_2) / \left(1 + \exp\left((DF_1 - a)/b\right)\right)$, and wherein DF_1 ~~is a type 1 diabetes feature that~~ represents an incidence of type 1 diabetes for the virtual patient so that values of DF_1 above a first threshold value correspond to an occurrence of type 1 diabetes in the virtual patient, DF_2 ~~is a type 2 diabetes feature that~~ represents an incidence of type 2 diabetes for the virtual patient so that values of DF_2 above a second threshold value correspond to an occurrence of type 2 diabetes in the virtual patient, H represents a degree of insulin resistance in a person with diabetes, and the parameters a and b are set to fit data for I, DF_1 and DF_2 for a population that is represented by the virtual patient.

Claim 74 (previously presented): The program storage device of claim 52, wherein the at least one value based on the virtual patient's FPG at time t is saved to a computer-readable medium.

Claim 75 (previously presented): The program storage device of claim 66, wherein the method further comprises:

setting values for the parameters a, b, c, and d by fitting the equation representing E to data for the population according to a least-squares criterion.

Claim 76 (new): The method of claim 1, wherein the virtual patient's FPG corresponds to a steady-state level of glucose after fasting by the virtual patient.

Claim 77 (new): The method of claim 3, wherein DF_2 reaches the threshold value at a time corresponding to an age of the virtual patient when the symptoms of type 2 diabetes first occur.

Claim 78 (new): The apparatus of claim 31, wherein the virtual patient's FPG corresponds to a steady-state level of glucose after fasting by the virtual patient.

Claim 79 (new): The apparatus of claim 33, wherein DF_2 reaches the threshold value at a time corresponding to an age of the virtual patient when the symptoms of type 2 diabetes first occur.

Claim 80 (new): The program storage device of claim 52, wherein the virtual patient's FPG corresponds to a steady-state level of glucose after fasting by the virtual patient.

Claim 81 (new): The program storage device of claim 66, wherein DF_2 reaches the threshold value at a time corresponding to an age of the virtual patient when the symptoms of type 2 diabetes first occur.

REMARKS

Claims 1–10, 31–40, 52 and 61–75 are pending in the present application. By this amendment, claims 3-5, 7-10, 33-35, 37-40, and 66-73 have been amended and claims 76-81 have been added. Accordingly, claims 1–10, 31–40, 52 and 61–81 are currently under consideration. Applicant respectfully submits that these claims are allowable.

No new matter has been added. Support for new claims 76-81 can be found, for example, at paragraphs 162, 163, and 169.

Applicant thanks Examiner Jason Sims for discussions on October 31, 2008, and November 5, 2008. The pending rejections, including the rejection based Van Holde (1996), were discussed for clarification purposes. No agreement was reached.

Claim Rejections under 35 USC § 112 (second paragraph)

Claims 3, 7, 10, 33, 40, 66, 70, and 73 and all claims dependent therefrom stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the office action, clearer claim wording is required with respect to limitations for *"DF_2"* (e.g., in claim 3). Claim 3 has been amended to recite *"DF_2 represents an incidence of type 2 diabetes for the virtual* patient*, so that values of DF_2 above a threshold value correspond to an occurrence of type 2 diabetes in the virtual patient."* Other claims have been similarly amended.

New claim 77 further recites *"*wherein *DF_2 reaches the threshold value at a time corresponding to an age of the virtual patient when the symptoms of type 2 diabetes first occur"*

That is, DF_2 characterizes whether or not the virtual patient has type 2 diabetes. For example, the embodiment discussed at paragraphs 162-163 of US 2005/0125158 A1, includes:

[0162] For type 1 diabetes, the feature DF_1 is a function of age, sex, family history, and race/ethnicity. For type 2 diabetes, the feature DF_2 is a function of age, sex, race/ethnicity, body mass index (BMI), and a factor that registers the effect of glucose intolerance. In an embodiment of the present invention, these formulas may be represented as follows

$$DF_1(t) = (1 - \exp(-\exp(a + bt + ct^2 + dt^3 + et^4 + gt^5)) \times famhist(\xi_1$$

$$DF_2(t) = \left(1 - \exp\left\{-\exp\left\{RGTG(\xi_2) \times \int\left(1 + \exp\left\{-\frac{(t - b)}{c}\right\}\right)\right\}\right\}\right) \times RBMI(BMI)(\xi_2$$

[0163] Race/ethnicity and sex are included through the values of the parameters a, b, c, d, e, and f. These equations may be scaled so that a person first begins to develop symptoms when $DF_1=1$ or $DF_2=1$. ξ_1 is a random value drawn from a uniform distribution on the interval (0, 1) hereinafter denoted as U[0, 1]. Drawing ξ_1 from U[0, 1] will cause the individuals in a large population (of a particular race/ethnicity/sex) to get type 1 diabetes at rates that match the observed age-specific incidence rates for that population, while allowing every individual to have a unique history of diabetes, including never getting type 1 diabetes. Similar intervals may be used for other values of ξ. famhis registers a patient's genetic propensity to develop the disease, based on their family history. It is set at birth and does not change.

That is, DF_2 can be scaled so that $DF_2(t)=1$ indicates the onset (or incidence) of type 2 diabetes at time t (e.g., age t). In this context one can interpret the above formula for DF_2 as $DF_2(t) = dF_2(t)/\xi_2$, where $dF_2(t)$ characterizes the *average* incidence of type 2 diabetes for the population (e.g., the probability of having type 2 diabetes by age t) and ξ_2 provides a random selection from the population (e.g., ξ_2 is selected from U[0,1]). The above example is illustrative, and other quantitative characterizations of type 2 diabetes are also possible.

As specified clearly in the claims, DF2 represents the incidence of type 2 diabetes for the virtual patient (e.g, $DF_2(t)=1$ at time t when the virtual patent gets diabetes).

According to the office action, clearer claim wording is required related to the limitations for *"wherein parameters a, b, c, and d are set* to *fit data for a population that is represented by the virtual patient"* (e.g., in claim 3). Claim 3 has been amended to recite *"wherein the*

parameters a, b, c, and d are set to fit data for E and DF_2 for a population that is represented by the virtual patient." Other claims have been similarly amended.

A population may be defined or characterized, for example as in the cited paragraphs 162-163 above, by "Race/ethnicitiy and sex" (as well as other characterizing features) and the virtual patient may be considered as a representative (or random selection) from the population. The parameters may be set by calculations based on data derived from the population (e.g., according to a *"least-squares criterion"* as further specified in claim 62), but alternatively other values may be used according to the requirements of the operational setting (e.g., testing through a range of parameter values).

Applicant respectfully requests that the above-cited rejection under 35 U.S.C. 112, second paragraph, be withdrawn.

Claim Rejections under 35 USC § 103

Claims 1–2 ,31–32, 52, 61, 63, 65, and 74 stand rejected under 35 U.S.C. 103(a) as being unpatentable over van Holde (1996). Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to on of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP § 2143) Applicant respectfully submits that that the Examiner has failed to present a *prima facie* case of obviousness.

Not All Claim Limitations Taught or Suggested

Claim 1 includes limitations for *"calculating the virtual patient's FPG at time t by solving an equation* $FPG(t) = FPG_0 / (1 * E)$." Applicant respectfully submits that the cited reference does not disclose or suggest these limitations and related limitations. In particular, the cited reference does not disclose or suggest quantitative characterizations generally or the specific limitations of the claims as applied to the quantitative characterizations.

Van Holde (1996) does not disclose or suggest quantitative characterizations generally. As noted in the Office Action, "Van Holde (1996) at page 824–825 teaches the role of insulin in the blood." However, as also noted in the Office Action, "Van Holde (1996) does not explicitly teach calculating the level of blood glucose according to the equation as is instantly claimed." In fact, there are no quantitative characterizations that can be related or identified with the limitations of the invention as claimed by claim 1. The Office Action points out only that "Van Holde (1996) at page 824–825 teaches the role of insulin in the blood," and "Van Holde (1996) at page 826–827 further teaches the relationship between blood glucose levels and insulin levels, such as if you increase insulin levels then blood glucose levels decrease and vice versa under normal circumstance."

Van Holde (1996) does not disclose or suggest specific limitations related to the quantitative characterizations. In particular, Van Holde (1996) does not disclose or suggest limitations for *"Fasting Plasma Glucose"* which relate to a more specific characterization than simply "glucose level in the blood." For example, paragraph 169 of US 2005/0125158 A1 includes:

> **[0169]** In the progression of diabetes, the development of signs, symptoms, and complications, and the response to treatments are determined primarily by the steady state level of glucose, which can be represented either by the fasting plasma glucose or HbA_{1c}. In the model, the FPG in a person with diabetes is determined by six variables that represent: the average FPG in people who do not have diabetes; hepatic glucose production; the effect of insulin resistance on hepatic glucose production; the insulin amount (I); the efficiency with which the body (liver, muscle, and fat) uses insulin (E); and the two primary diabetes features (DF_1 and DF_2). In people who develop type 3 diabetes, the simulated liver cells develop a resistance to the effects of insulin. This causes the simulated liver to produce too much glucose. In response, the simulated beta cells produce more insulin. Over time, this compensatory mechanism begins to fail, through a combination of decreased insulin production (e.g., "beta cell fatigue"), and increasing resistance to insulin by the liver. In addition, the uptake of glucose by the simulated muscles and fat gradually decreases due to insulin resistance affecting those organs. Taken together, these factors create a relative deficiency of insulin, with resulting increases in glucose. In an embodiment of the present invention, these relationships may be addressed as follows.

The cited reference contains no disclosure directed towards *"Fasting Plasma Glucose(FPG)"* (e.g., as a characterization of "the steady state level of glucose") together with

related quantities *"basal hepatic production (FPG_0),"* *"insulin level (I),"* *"efficiency of insulin use"* *"E"*, for *"outputting at least one value for the virtual patient's FPG at time t to a user."*

Applicant respectfully submits that the Examiner has improperly relied upon inherency in support of the rejection. That is, the equation specified by the claim limitations are not directly or indirectly disclosed by the cited reference. In particular, the Examiner has ignored limitations related to *"Fasting Plasma Glucose(FPG)"* (e.g., as a characterization of "the steady state level of glucose" as described in par. [0069]) together with other claim limitations.

Reliance on inherency when the reference is silent about the asserted inherent characteristic requires a rationale or evidence showing inherency. MPEP § 2112. The rationale or evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 169 F.3d 743, 745 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); (MPEP § 2112>IV).

Improper Combination or Modification of References

According to the Office Action, "It would have been obvious to one of ordinary skill in the art to mathematically represent the calculation of a fasting blood glucose level as being indirectly proportionate to the level of insulin as Van Holde (1996) has clearly described in the recited pages. It has been well known by those of ordinary skill in the art that under normal circumstances, if one increases the level of insulin in the blood that its effect is to decrease the glucose level in the blood. It is common to those of ordinary skill in the art to represent such relationships generically and mathematically as an indirect relationship." (emphasis added)

As discussed above, the rejection ignores limitations of the claims (e.g., *"Fasting Plasma Glucose(FPG)"* as a characterization of "the steady state level of glucose") and provides no motivation for modifying the reference to achieve the invention as claimed. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. (MPEP 2143.01)

In this case, the rejection relies on "common knowledge" without any apparent support. It is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record as the principal evidence upon which a rejection is based. "[T]he Board cannot simply reach conclusions based on its own understanding or experience -- or on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings." (*In re Zurko*, 258 F.3d 1379, 1385 (Fed. Cir. 2001)) (MPEP 2144.03)

No Reasonable Expectation of Success

According to the Office Action, "It has been well known by those of ordinary skill in the art that under normal circumstances, if one increases the level of insulin in the blood that its effect is to decrease the glucose level in the blood. It is common to those of ordinary skill in the art to represent such relationships generically and mathematically as an indirect relationship." (emphasis added)

Applicant respectfully submits that a general understanding of behavior "under normal circumstances" together with general principles "to represent such relationships generically and mathematically" provides no reasonable expectation of success for the modifications proposed with respect to this rejection. The Examiner has not demonstrated a "degree of predictability" sufficient to support this rejection. (MPEP 2143.02)

Additionally, the condition that "under normal circumstances, if one increases the level of insulin in the blood that its effect is to decrease the glucose level in the blood" does not apparently even apply to an evolution of *"Fasting Plasma Glucose(FPG)."*

Argument Conclusion

The above-cited characteristic features of the present invention as claimed by claim 1 are not disclosed or suggested by the cited reference. Therefore, claim 1 is allowable over the cited reference. Claims dependent from claim 1 are likewise allowable over the cited reference. Corresponding apparatus claims are likewise allowable including claim 31 and its dependent claims. Corresponding program storage device claims are likewise allowable including claim 52 and its dependent claims.

Further, claim 2 includes limitations *"wherein E is scaled such that E = 1 in the absence of diabetes and 0≤E<1 in the presence of diabetes."* As discussed above with respect to claim 1, the cited reference does not disclose or suggest this limitation. For example the Office Action does not point out any quantitative characterization of efficiency or even any specific discussion of efficiency in the cited reference. Similar arguments apply for related limitations in apparatus claim 32 and program storage device claim 65.

Further, as discussed above, the cited reference does not disclose specific limitations related to *"Fasting Plasma Glucose(FPG)."* New claims 76, 78, and 80 further recite *"wherein the virtual patient's FPG corresponds to a steady-state level of glucose after fasting by the virtual patient."*

Applicant respectfully requests that the above-cited rejection under 35 U.S.C. 103(a) be withdrawn.

CONCLUSION

In view of the above, Applicant respectfully submits that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

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In the unlikely event that the transmittal letter is separated from this document and the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 04-1679** referencing **Docket No. R1390-00003**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 10, 2008

Respectfully submitted,

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